REMARKS/ARGUMENTS

Claims 34 – 36 and 38 – 50 are pending in the application. Claims 46 – 50 are withdrawn as drawn to a non-elected invention, pursuant to a restriction requirement.

The Office Action objects to the disclosure because of the following informality: not having appropriate section headings in the Specification. However, the Preliminary Amendment filed on May 4, 2005, amended the Specification to provide appropriate section headings, including "Discussion of the Background Art," "Summary of the Invention," "Brief Description of the Drawings," and "Detailed Description of the Preferred Embodiment." Therefore, Applicants request reconsideration and withdrawal of the objection regarding subject headings.

Claims 34 – 36, 38 – 42 and 44 are rejected under 35 U.S.C. §103(a) as unpatentable over U.S. Patent Application Publication No. 2002/0004065 to Kanios (hereinafter, "Kanios").

As acknowledged in the Office Action, "Kanios does not explicitly prepare a composition with rifaximin and PVA." Thus, Kanios fails to disclose two technical features of the claimed device.

Furthermore, it should be noted that Kanios relates to transdermal drug delivery systems providing substantially zero order release profiles for an extended period of time of up to seven days or longer (see paragraphs [0001] and [0020] – [0024]).

In view of this object, Kanios discloses (in Claim 1): "A transdermal delivery system for delivery of a therapeutically effective amount of an active agent comprising:

> (a) a pharmaceutically acceptable pressure-sensitive adhesive matrix carrier composition,
>
> (b) one or more polymeric plastic materials which are substantially insoluble in water in an amount up to 30%, said amount being sufficient to provide a substantially zero-order drug release profile in excess of 72 hours,
>
> (c) one or more active agents,
>
> (d) a crystallization inhibitor capable of absorbing and holding water, and
>
> (e) optionally, one or more solvents, co-solvents and permeation enhancers." [emphasis added]

Therefore, not only does Kanios fail to disclose two relevant technical features of the present claims, but Kanios does not pertain to the same field of endeavor as the current claims.

As a matter of fact, Kanios clearly refers as follows [emphasis added]:

> "[0009] While matrix-type devices, especially drug-in-adhesive devices, have achieved more uniform and controlled drug deliver rates, and for longer periods of time, most transdermal systems remain subject to a higher initial drug release than is required to achieve therapeutic efficacy. For many drugs and/or therapeutic situations, it wold be advantageous to eliminate or suppress this higher initial release and achieve a "steady state" (zero order) release profile which uniformly delivers a therapeutically effective amount of drug over the extended duration of device's desired use.
>
> [0010] For example, the high initial release of certain drugs may cause adverse or undesired effects, or create toxicity concerns, thereby foreclosing the use of transdermal administration. In other instances, the higher initial release may reduce the amount of drug required for treatment to the point of risking underdosing, or may make it impractical to try and increase the

> duration of the device's application while retaining therapeutic effectiveness. The ability to reduce the frequency of replacing the transdermal drug delivery system would concomitantly increase user compliance, reduce any lag or drop off in efficacious blood levels, and reduce the amount of drug required for treatment (also provided by reducing the higher initial blood level associated with the higher release rate).
>
> [0011] Therefore, despite the existence of many different types of transdermal delivery systems in the art, there remains a continuing need for improving the release profile of drugs to achieve substantially zero order, as well as extending the duration of use of each transdermal system." [emphasis added]

Thus, the resulting transdermal delivery system of Kanios has been designed to achieve substantially zero order of the drug release profile, independently of the type of drug in use.

It should be noted that Kanios discloses a practically unlimited list of possible active agents to be delivered (i.e., paragraphs [0056] to [0349]).

Additionally, when Kanios at paragraph [0046] discloses the crystallization inhibitor, another practically unlimited list of possible substances is given, as it is stated that any "...absorptive agents that possess the capability to absorb and hold water or moisture" can be used. However, in the subsequent paragraphs [0047] to [0053], as well as in the Examples, only PVP is actually further described for use as the crystallization inhibitor.

Therefore, a person having ordinary skill in the art at the time the invention was made would have not considered Kanios, because Kanios pertains to a different field of endeavor, as demonstrated above; but, in the hypothetical case where he/she would have considered Kanios, the only available information would have been:

– the transdermal delivery system of Kanios is designed to eliminate or suppress the higher initial release of drug and achieve a "steady state" (zero order) release profile in order to avoid the risk of underdosing and/or reducing the duration of the device's desired use;

– said system includes:

(a) a pharmaceutically acceptable pressure-sensitive adhesive matrix carrier composition,

(b) one or more polymeric plastic materials which are substantially insoluble in water in an amount up to 30%, said amount being sufficient to provide a substantially zero-order drug release profile in excess of 72 hours,

(c) one or more active agents, (that can be any active agent, as above reported)

(d) a crystallization inhibitor capable of absorbing and holding water,

(however, only a polyacrylate/polysiloxane adhesive blend with 10% PVP is exemplified in Kanios), and

(e) optionally, one or more solvents, co-solvents and permeation enhancers.

– notwithstanding the practically unlimited lists of possible substances in Kanios, the exemplified systems only include:

· a polyacrylate/polysiloxane adhesive blend with 10% PVP,

· ethyl cellulose,

· dipropylene glycol,

· oleyl alcohol, and

· at most two active agents; i.e., estradiol and/or norethindrone acetate.

In this regard, the person having ordinary skill in the art would have never been aware of the specific and peculiar problem involved with the use of rifaximin, nor found in Kanios any useful information in order to solve the same.

Conversely, the current disclosure advantageously discloses devices that make possible the use of rifaximin "...outside the intestine (e.g., in the oral and pharyngeal or nasal cavities, in the rectum or vagina). In particular, they allow high-level, constant in time, of concentration of rifaximin in aqueous body fluids avoiding the intense red color that it produces in the neighboring [areas] of the place of [administration]." (see page 2, lines 23 – 26).

This means that a person having ordinary skill in the art would have never taken into consideration Kanios, teaching how to eliminate or suppress the higher initial release of drug, for solving the problem of the administration of high level, constant in time, of concentration of rifaximin in aqueous body fluids avoiding the intense red color that it produces in the neighboring [areas]. As a matter of fact, there was no suggestion concerning the specific problem of rifaximin among the myriad of active agents listed by Kanios, and consequently no motivation to search in the direction of the current claims.

Consequently, this highlights even more the criticality of the claimed combination of the percentage of rifaximin and the bi-phasic material, "wherein in said bi-phasic material the solid phase is an elastic polymeric matrix comprising polyvinylalcohol, and the liquid phase is water that fills up the pores of said matrix," as in claim 34 [emphasis added], is clearly not

recognizable nor derivable from Kanios.

Thus, Applicants submit that the present claims could not be considered a result of routine optimization by a person having ordinary skill in the art, as asserted in the Office Action, when the relevant lists disclosed in Kanios are practically unlimited, and the Examples include different substances designed for different purposes.

Indeed, Applicants submit that the conclusions reached in the Office Action require impermissible hindsight in order to arrive at the present claims, as there would have been no basis to have arbitrarily selected substances from the practically unlimited lists in Kanios.

In other words, a person having ordinary skill in the art at the time of the invention, with knowledge of the disclosure in Kanios, would not have recognized in rifaximin a problematic active agent among the very large numbers of active agents listed, nor recognized the solution in a bi-phasic material, wherein the solid phase is an elastic polymeric matrix comprising polyvinylalcohol, and the liquid phase is water that fills up the pores of the matrix, as in the present claims.

Therefore, for all of the above reasons, claim 34 is not obvious over Kanios.

Dependent claims 35, 36, 38 – 42, and 44, for at least the same reasons as presented for claim 34, are likewise neither disclosed nor suggested by Kanios.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the §103(a) rejections over Kanios to claims 34 – 36, 38 – 42, and 44.

Claims 34 – 36 and 38 – 44 are rejected under 35 U.S.C. §103(a) as unpatentable over Kanios, in view of U.S. Patent No. 4,908,213 to Govil, et al. (hereinafter, "Govil et al.").

Govil et al. disclose a transdermal drug delivery patch; in particular, a patch useful for the transdermal delivery of nicotine. The patch comprises "...an amount of nicotine or a pharmaceutically acceptable salt or solvate thereof effective to treat symptoms associated with tobacco smoking cessation and an amount of an antipruritic effective to treat the pruritis associated with transdermal delivery of nicotine, in a pharmaceutically acceptable carrier," (see Claim 1). The antipruritic agent can be bisabolol, oil of chamomile, chamazulene, allantoin, D-panthenol, glycyrrhetenic acid, corticosteroids and antihistamines.

The Office Action at page 7 states that "Govil et al. discloses that pharmaceutically acceptable pressure sensitive adhesives such as acrylic polymers can be used alone or in combination with the active ingredient to prepare an adhesive drug matrix or may be applied to the skin contacting surface of a polymeric matrix (col. 3, lines 10 – 18). Suitable polymeric matrix materials include PVA and PVP (col. 3, lines 49 – 52)."

However, there would not have been any reason why a person having ordinary skill in the art, at the time of the invention, would have combined Kanios, regarding a system designed to eliminate or suppress the higher initial release of drug and achieve a "steady state" (zero order)

release profile, with Govil et al., regarding a patch comprising nicotine and at least one antipruritic compound useful for reducing or eliminating itching caused by the transdermal penetration of nicotine, in order to address and solve the specific problem of rifaximin.

Even if a person of ordinary skill in the art had, hypothetically, combined the two cited art documents, he/she would have been led, at most, to believe that, when nicotine is used as an active agent, the transdermal delivery system of Kanios has to further include at least one antipruritic compound.

Thus, for at least the above reasons, Applicants submit that claim 34 is also not obvious over Kanios, in view of Govil et al.

Likewise, dependent claims 35, 36, 38 – 42, and 44 would not have been obvious over the combination of Kanios and Govil et al., for at least the same reasons as presented above.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the §103(a) rejections over Kanios and Govil et al. to claims 34 – 36 and 38 – 44.

Claims 34 – 36, 38 – 42, 44, and 45 are rejected under 35 U.S.C. §103(a) as unpatentable over Kanios, in view of U.S. Patent No. 6,194,455 to Wharton (hereinafter, "Wharton").

Wharton discloses a composition and method for treating skin ulcers with a sucralfate in combination with a topical anesthetic. In its sole claim, Wharton discloses, a "method of

preventing a nascent herpes outbreak from developing into a herpes ulcer, comprising the topical administration of a composition as a prophylactic comprising sucralfate and lidocaine in a weight:weight ratio of from about 500:1 to about 200:1, respectively, and a pharmaceutically effective amount of an antibiotic, in a pharmaceutically acceptable carrier to a site identified as a nascent herpes outbreak." (see Claim 1) [emphasis added].

Wharton clearly does not pertain to the same field of endeavor as in the current claims.

The Office Action, at page 8, states, in part, that "It would have been obvious to one of ordinary skill in the art at the time of the instant invention to prepare a topical, transdermal composition as taught by Kanios and to include additional active agents."

As noted above, Kanios had already discloses the possibility to include in its system "one or more active agents" (also in Claim 1 of Kanios), and practically unlimited lists of substances as "active agent," such that the person having ordinary skill in the art would not have found disclosed in Wharton any additional information with respect to what had already been disclosed by Kanios.

Therefore, the arguments provided above with respect to Kanios would also apply to the combination of Kanios and Wharton. Accordingly, claim 34 is not obvious over Kanios, in view of Wharton.

Dependent claims 35, 36, 38 – 42, 44, and 45 would also not be obvious over Kanios, in

view of Wharton, for at least the same reasons as presented above.

Thus, for all of the above reasons, Applicants submit that claims 34 – 36 and 38 – 45 are not obvious over the cited art, either taken alone or combined with each other, and are in condition for allowance. Accordingly, Applicants respectfully request issuance of a Notice of Allowance for claims 34 – 36 and 38 – 45.

Respectfully submitted,

9/8/09
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